PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
CAROL TALKINGTON VERSER
HESKA CORPORATION
1613 PROSPECT PARKWAY
FORT COLLINS, CO 80525

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	17 FEB 2005
Applicant's or agent's file reference DI-13-C6-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US04/09135	25 March 2004 (25.03.2004)	27 March 2003 (27.03.2003)

International Patent Classification (IPC) or both national classification and IPC

IPC(7): GO 1N 33/53 and US Cl.: 435/7

Applicant

HESKA CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☒ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☒ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450	Deborah A Davis
Facsimile No. (703) 305-3230	Telephone No. (572) 272-0818

Form PCT/ISA/237 (cover sheet) (January 2004)

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Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 5,6 and 8

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5,6 and 8 are so unclear that no meaningful opinion could be formed *(specify)*:

No meaningful search could be established for the above claims because the names of these antibodies are not art recognized. (PCT Rule 6.4(a))

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims NONE	YES
	Claims 1-17	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-17	NO
Industrial applicability (IA)	Claims 1-17	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-3, 7, 9-11, 15-17 lack an inventive step under PCT Article 33(3) as being obvious over Suzuki et al (USP#4,246,835) in view of Lau (USP#5,087,575), in view of Zimmerle (USP#5,043,744) further in view of Zimmerle (USP#5,403,744) and in further view of Zhang et al (USP#6,214,813).

Suzuki et al teaches a method of diagnosing renal disease by detecting fragments of albumin in human urine. The detection is carried out by immunological methods (see abstract), such as EIA and immunoblot techniques (column 2, lines 63-68). All protein contained in a urinary sample to be assayed are solubilized by treating the sample in boiled water for a certain period to inactivate the proteases contained in the sample (column 4, lines 45-55). Separated human albumin and the human albumin fragments are transferred to a support and visualized by utilizing an immunoblot method (column 3, lines 35-40). Detection was carried out at room temperature (column 13, lines 17-35). Suzuki et al also teaches accurate quantitative determination of urinary albumin may be carried out by RIA and inmunoprecipitation with commercially available kits that contains anti-albumin antibodies and albumin-immunized latex, wherein latex is agglutinated by the antigen-antibody reaction (column 1, lines 29-46).

Suzuki et al is silent with respect to teaching the particular ranges of albumin levels is diagnostic of renal disease.

However, the reference of Lau teaches that the concentrations of protein in urine should be minimal to non-existent because abnormally high amount of albumin and/or low-molecular weight proteins in urine must be detected and related to a renal disease (column 1, lines 49 - column 2, lines 1-15). Lau discloses a method of assaying urine for proteins at low to trace quantities ranging from 0 mg/dL to 2000mg/dL (columns 6 and 7) which encompasses albumin ranges in the instant invention. Lau utilizes test strips (dipstick-base assay) that are dipped into urine samples that has a dye indicator and for each albumin concentration; the specific gravity of a urine sample was adjusted from 1.007 to 1.032 (column 22, lines 47-67).

Lau does not teach the specific gravity of urine is indicative of renal disease.

However, the reference of Zimmerle teaches that abnormally high or low specific gravities are clinically significant. But, urine with a fixed low specific gravity of approximately 1.010 that varies little from specimen to specimen is known as isothenuric which is a condition indicative of severe renal damage with disturbance of both the concentrating and diluting abilities of the kidney.

Zimmerle does not teach obtaining a urine sample from a felid or equid to determine the amount of albumin.

However, Zhang et al. teaches a method of lowering protein levels in urine, by administering to a patient an effective amount of a compound or pharmaceutical composition orally, intravenously or around the kidney (page 9, paragraph 0121). These pharmaceuticals are therapeutic. The patient of interest could be felines, equines, canines (page 7, paragraph 0096) used in animal models for experimental investigations of human disease.

It would have been obvious to one of ordinary skill in the art to modify the reference to Suzuki et al to include the correlation of particular albumin concentration ranges as taught by Lau because differentiating between low protein concentration levels is clinically important in the art because a range of from about 10mg/dL to about 20mg/dL is used as the normal urine protein level for a healthy individual, therefore urine protein levels from 0 mg/dL to 10mg/dL may indicate an excessive excretion of proteins that can signify a diseased state. It would have been further obvious to one of ordinary skill in the art to modify the reference of Suzuki et al to include the teaching of specific gravity at the range of 1.010 as taught by Zimmerle, to identify patients with severe renal damage. It would have been further obvious to one of ordinary skill in the art to determine albumin levels in the urine of felids and equids because they are used as animal models for experimental investigations to explore human disease.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Claims 12-14 an inventive step under PCT Article 33(3) as being obvious over Suzuki et al, in view of Lau, in view of Zimmerle, in view of Zhang et al, and further in view of Morrison et al (USP#804,625).

The teachings of Suzuke et al, in view of Lau, in view of Zimmerle, in view of Zhang et al are set forth above but does not specifically mentions the use of enzyme-linked assays and a single-step.

However Morrision et al teaches assay procedures for ELISA's and homogeneous (single step) assays. Morrison discloses that as many as 2,000 assays by a technician employing a solid-phase ELISA in microtiter plates and these thpes of assays can be performed in a homogeneous assay (single step) format which bound and free labeled material need not be separated (column 2,k lines 9-32).

Therefore, it would have been obvious to one of ordinary skill in the art to modify the teachings of Suzuki et al, in view of Lau, in view of Zimmerle, in view of Zhang et al above to include homogeneous (single step) and ELISAs assay formats as taught by Morrison et al because detection of analytes can be performed without laborious separation steps (column 2, lines 9-32).

Claim 4 lack an inventive step under PCT Article 33(3) as being obvious over Suzuki et al (USP#4,246,835) in view of Lau (USP#5,087,575), in view of Zimmerle (USP#5,043,744) in view of Zimmerle (USP#5,403,744) in view of Zhang et al (USP#6,214,813) and further in view of Zuk et al (USP#4,281,061).

Zuk et al teach as a matter of convenience the reagents can be provided as kits, where the reagents are in predetermined ratios, so as to substantially optimize the sensitivity of the assay in the range of interest (column 2, lines 63-66). Further, the reagents in a kit are available in pre measured amounts which eliminates the variability that can occur when performing the assay.